MONOGRAPH

PHENYTOIN

Scope (Staff):	Medical, Pharmacy, Nursing, Anaesthetic Technicians
Scope (Area):	All Clinical Areas

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this DISCLAIMER

⚠ HIGH RISK MEDICINE ⚠

QUICKLINKS

Dosage/Dosage Adjustments	Administration	Compatibility	Monitoring

DRUG CLASS

Phenytoin is an anticonvulsant medication which acts primarily on the motor cortex and also affects other parts of the brain.[1] It prevents repetitive neuronal discharges by blocking voltage-dependent and use-dependent sodium channels.[1, 2]

Phenytoin is a High Risk Medicine.

INDICATIONS AND RESTRICTIONS

- Treatment of epilepsy, including simple and complex partial (focal) seizures and generalised tonic clonic seizures.[2, 3]
- Seizure prophylaxis in neurosurgery and traumatic brain injury.[2, 3]
- Status epilepticus (usually administered IV).[2, 3]

CONTRAINDICATIONS

- Hypersensitivity to phenytoin or any component of the formulation.[3]
- Pregnancy – Category D.[3]

- Acute porphyrias.[3]
- Sinus bradycardia, sinoatrial block, second and third degree atrioventricular block, Stokes-Adams Syndrome – IV phenytoin contraindicated.[3]

PRECAUTIONS

- A small change in dosage may result in a disproportionately large change in phenytoin concentration due to saturation of its hepatic metabolism.[2, 3]
- Measurement of free phenytoin (not bound to albumin) is recommended in patients with decreased albumin concentration or in patients with chronic renal failure.[2, 3]
- Phenytoin should be weaned off gradually unless there are safety concerns as abrupt withdrawal may precipitate status epilepticus.[4, 7]
- Diabetes – Risk of hyperglycaemia.[3]
- Treatment with levothyroxine (thyroxine) – phenytoin may increase its metabolism; increase in levothyroxine dose may be necessary.[3]
- Asian ancestry (especially Han Chinese, Thai, Malay) – more likely to have HLA-B*1502 allele, which significantly increases the risk of severe skin reactions.[3]
- History of Severe Cutaneous Adverse Reaction (SCAR) such as Stevens Johnson Syndrome with use of antiepileptic drugs with aromatic ring structure (e.g. Carbamazepine, oxcarbazepine, lamotrigine and phenobarbital [phenobarbitone]) – consult neurologist's advice before administering phenytoin.[3, 7]

FORMULATIONS

Listed below are products available at PCH, other formulations may be available, check with pharmacy if required:

Phenytoin:

- *Chewable Tablets* - phenytoin 50mg (Dilantin **Infatabs**®)[3]
- *Oral liquid* - phenytoin oral suspension 20mg/mL (AUSPMAN) **Note: Phenytoin suspension (Dilantin®) 30mg/5mL is NOT AVAILABLE at PCH**

Phenytoin sodium:

- *Capsules* – phenytoin sodium 30mg and 100mg (Dilantin®)[3]
- *Injection* – phenytoin sodium 50mg/mL (2mL or 5mL)[3]

Phenytoin Injection and Phenytoin Capsules **MUST** be prescribed as **Phenytoin SODIUM**

For the purpose of dose conversion calculation, 100mg phenytoin sodium is equivalent to approximately 90mg phenytoin.[1]

Example of dose conversion between phenytoin and phenytoin sodium:

- Converting from Phenytoin SODIUM to Phenytoin

Phenytoin dose (mg) = Phenytoin SODIUM (mg) X 0.9

- Converting from Phenytoin to Phenytoin SODIUM

  Phenytoin SODIUM dose (mg) = Phenytoin (mg) X 1.1

- Imprest location: Formulary One

DOSAGE & DOSAGE ADJUSTMENTS

Neonates: Refer to Neonatal Medication Protocols

The following doses are within the standard reference range. Higher doses may be prescribed under the direction of a neurology fellow/consultant for certain situations.

Dosing in Overweight and Obese Children: Loading doses should be calculated using adjusted body weight and all maintenance doses using Ideal Body Weight. Please refer to "Guidelines for Drug Dosing in Overweight and Obese Children 2 to 19 Years of Age".

Partial (focal) seizures, generalised tonic clonic seizures:

*If a loading dose has been given, maintenance dosing is usually started 12-24 hours later.[1, 4]

- **1 month to 12 years:**

  Oral or IV: initially 3-5mg/kg daily in 2-3 doses, adjust according to response and plasma phenytoin concentration to usual maintenance dose of 4-8mg/kg daily in 2-3 doses (maximum 300mg daily).[1, 3]

- **12-18 years:**

  Oral or IV: initially 4-5mg/kg (or 150-300mg) daily in 1-2 doses; increase gradually according to response and plasma phenytoin concentration to usual maintenance dose of 200-500mg daily in 2-3 doses (usual maximum 600mg daily in 2 doses).[1, 3]

Status epilepticus:

- **1 month to 18 years**:

  IV: 10-20mg/kg.[3,5,8,9]

  - Infuse over 20 minutes if the dose is 1000mg or less.[11, 12]
  - Infuse over 30 minutes if the dose is greater than 1000mg, up to a maximum of 1500mg[11, 12]

  A 20mg/kg dose should be given in the Emergency Department in patients experiencing severe seizures.

  Consider Intraosseous route if IV route is unavailable.

  Consider reducing the dose to 5-10mg/kg, for patients already taking phenytoin.[1]
  Maximum dose 1500mg.[8]

Concentration monitoring is recommended when changing from a product containing phenytoin to another product containing phenytoin sodium (and vice versa); adjust dosage if necessary.[1]

Hepatic impairment:

- May require dosage adjustment.[3]

RECONSTITUTION & ADMINISTRATION

ENTERAL:

- Give at the same time with regard to food (always with or always without food) but do *not* give at the same time as enteral feeds due to decreased absorption of phenytoin. [1,3]
- For patients on enteral feeds, stop feed two hours before administration of phenytoin, during and for two hours after administration of phenytoin; IV phenytoin may be preferred if enteral feeding cannot be interrupted.[3]
- If administering via an enteral feeding tube, dilute oral liquid with water and ensure that the tube is flushed thoroughly before and after administration.[3]

INTRAVENOUS INFUSION:

- Prepare infusion immediately before use.[5]
- Flush IV lines with sodium chloride 0.9% before and after phenytoin infusion.[5]
- Withdraw required dose and dilute with sodium chloride 0.9% to give a final concentration of 5mg/mL.[5,10]
- Phenytoin is poorly soluble and may precipitate when diluted.[5]
- Inspect solution for particles and **ONLY** use solutions that are clear and do not contain particles. Check for haziness throughout the infusion.[6]
    - Use a 0.2–0.5 micrometre inline filter if possible.[5]
- Infuse over at least 20 minutes for doses less than 1000mg and over 30 minutes for doses between 1000mg-1500mg.[11, 12]
    - Administration at faster rates may result in cardiac arrhythmias, impaired cardiac conduction, hypotension, cardiovascular collapse or CNS depression.[5]
- In fluid restricted patients phenytoin may be given at higher concentrations or given undiluted providing that the maximum rate of infusion (above) is not exceeded.[5]

IM injection : NOT RECOMMENDED, slow and erratic absorption and risk of tissue necrosis.[5, 6]

COMPATIBILITY *(LIST IS NOT EXHAUSTIVE)*

Compatible fluids:

- Compatible with sodium chloride 0.9% (for up to 2 hours) ONLY.[5]
    - Not compatible with glucose or other fluids.[5]
- The addition of phenytoin to other infusion fluids is not recommended due to lack of stability and resultant precipitation.[5]

Do not mix with other medications.[5]

MONITORING

- IV loading dose:
    - Continuous Electrocardiogram (ECG).[3,5]

  - Blood pressure, heart rate, respiratory rate, oxygen saturation every 5 minutes during infusion and for 30 minutes after completing the flush.
  - If bradycardia or hypotension occurs, stop the infusion and contact the doctor; consider recommencing infusion at a lower rate once patient has stabilised. [3,5]

- Therapeutic range:
  - Total phenytoin = 10-20mg/L (trough level).[2, 3, 8]
  - Free phenytoin = 1-2mg/L (trough level); recommended in patients with decreased albumin or with chronic renal failure.[3]
  - Steady state concentration is reached in 5-10 days unless therapy is initiated with a loading dose.[2, 3, 8]
- Small changes in phenytoin dosage may result in disproportionately large changes in concentration due to non-linear pharmacokinetics and saturation of its hepatic metabolism.[3, 9]
- Monitoring for adverse events (hypotension, arrhythmias [IV use], ataxia, nystagmus).[2, 3]
- Stop treatment immediately if skin reaction or signs of hypersensitivity occur. If stopping treatment for other reasons reduce dose gradually.[2, 3]
- **If bradycardia or hypotension occurs, stop the infusion and call the doctor. Consider recommencing infusion at a lower rate.**
- Extravasation may cause necrosis. Monitor the injection site closely.[5]

ADVERSE EFFECTS

Common: nausea, vomiting, insomnia, agitation, sedation, confusion, ataxia, nystagmus, diplopia, blurred vision, vertigo, behavioural disturbances, impaired learning (dose related), gingival hypertrophy, skin eruptions, coarse facies, hirsutism (long term use). [3]

IV: hypotension, thrombophlebitis, local skin reactions including necrosis and purple glove syndrome (distal limb oedema, discolouration, pain). Rapid administration may result in cardiac arrhythmias and cardiovascular collapse.[5, 6]

Rare: hepatotoxicity (usually as part of multi-organ hypersensitivity syndrome), hallucinations, peripheral neuropathy, choreiform movements, cerebellar atrophy, blood dyscrasias, hyperglycaemia, osteomalacia and rickets, Steven-Johnson syndrome, toxic epidermal necrolysis, systemis lupus erythematosus. [1, 3]

STORAGE

Ampoules:

- Protect from light, store below 25°C.[5]
- Precipitation may occur if the ampoule is refrigerated or frozen but will dissolve at room temperature and is still suitable for use. A faint yellow colour may develop but potency is not affected.[5]

Diluted solution:

- The infusion must be used immediately after dilution.[5]

COMMENTS

Consider bone mineral density monitoring, and vitamin D and calcium supplements to prevent osteomalacia and osteoporosis, in patients on long-term treatment, particularly those at higher risk.[3]

INTERACTIONS

This medication may interact with other medications; consult PCH approved references (e.g. Clinical Pharmacology), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

Please note: The information contained in this guideline is to assist with the preparation and administration of **phenytoin**. Any variations to the doses recommended should be clarified with the prescriber prior to administration

References

1. Australian Medicines Handbook Children's Dosing Companion Adelaide: Australian Medicines Handbook; 2018 [cited 2018]. Available from: https://childrens-amh-net-au.pklibresources.health.wa.gov.au/.
2. Mims Online 2018 [updated December 2018; cited 2018]. Available from: https://www-mimsonline-com-au.pklibresources.health.wa.gov.au/Search/Search.aspx.
3. Australian Medicines Handbook Australia2018 [cited 2018]. Available from: https://amhonline-amh-net-au.pklibresources.health.wa.gov.au/.
4. Micromedex I. Phenytoin 2021 [19 Oct 2021]. Available from: http://www-micromedexsolutions-com.pklibresources.health.wa.gov.au/micromedex2/librarian
5. Australian Injectable Drugs Handbook, 7th Edition: Health Communication Network; 2018 [updated 14/11/2018]. Available from: https://aidh-hcn-com-au.pklibresources.health.wa.gov.au/browse/about_aidh.
6. Paediatric Injectable Guidelines Melbourne, Vicotria: Royal Children's Hospital, Melbourne; 2018. Available from: https://pig-rch-org-au.pklibresources.health.wa.gov.au/monographs/zoledronic-acid/.
7. UpToDate: Wolters Kluwer; 2018. Available from: https://www-uptodate-com.pklibresources.health.wa.gov.au/contents/search.
8. Elsevier. Clinical Pharmacology: Elsevier; 2018 [cited 2018]. Available from: http://www.clinicalpharmacology-ip.com.pklibresources.health.wa.gov.au/default.aspx?id=24317714.
9. Williams. S (Neurologist). [Consensus Expert Opinion]. Perth Children's Hospital. March 2019.
10. Royal Children's Hospital Melbourne Paeditric Injectable Guidelines Online https://pig.rch.org.au/2021/10/updated-monographs-2021/ Cited July 2022.
11. Lyttle MD, Rainford NE, Gamble C, Messahel S, Humphreys A, Hickey H. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial - The Lancet. April 17, 2019.
12. Dalziel SR, Borland M, Furyk J, Bonisch M, Neutze J, Donath S. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial - The Lancet. April 17 2019.

Useful resources (including related forms)
Australian Medicines Handbook-Children's Dosage Companion
Clinical Practice Manual – IV Access Monitoring and Maintenance (Extravasation Guide)
Peripheral Intravenous Cannula (PIVC) Insertion and Management
Martindale Complete Drug Reference: Phenytoin

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